DECLARATION EVIDENCE

Declarations providing supportive evidence for the subject reexamination response and rebuttal of certain conclusions reached in the pending Office Action are submitted concurrently herewith. The declarations are as follows:

A. Declaration of Margaret A. Wheatley (including Exhibit 1-3) (hereinafter referred to as the "Wheatley Declaration").

B. Declaration of Michael R. Violante (including Exhibit 1) (hereinafter referred to as the "Violante Declaration").

C. Declaration of Jerry L. Atwood (including Exhibits 1-2) (hereinafter referred to as the "Atwood Declaration").

D. Declaration of James D. Lear (including Exhibits 1-5) (hereinafter referred to as the "Lear Declaration").

E. Declaration of Michel Schneider (including Exhibit 1-2) (hereinafter referred to as the "Schneider Declaration").

F. Declaration of Richard D. Chambers (including Exhibit 1) (hereinafter referred to as the "Chambers Declaration").

Each declaration is labeled with the name of the declarant, and the declarations and any exhibits thereof, as summarized in the Table of Declarative Evidence, are attached hereto.

RESPONSE TO THE OFFICE ACTION

A. Administrative Notice

In the beginning of the Office Action, the Examiner refers to "administrative notice" regarding the terms microbubbles, microballoons, microparticles, microspheres, gas bubbles, microcapsules, and gas filled liposomes and their use in the art. Specifically, the Examiner notes that these terms "have been used so interchangeably" in the art "as to render them indistinguishable from one another," and concludes that patentability of Applicants' claims

will "hinge on the particular materials" recited therein, rather than on Applicants' recitation of the term "microsphere" in those claims. *See* Office Action, p. 2.

1. The Terms "Microbubbles," "Microballoons," "Microparticles," "Microspheres," "Gas Bubbles," "Microcapsules," "Gas-Filled Liposomes," Etc., Are Not *Per Se* Interchangeable.

The Examiner's assertion that the terms microbubbles, microballoons, microparticles, microspheres, gas bubbles, microcapsules, gas filled liposomes, and the like, are necessarily interchangeable and, therefore, indistinguishable, is inaccurate.

At the outset, it is axiomatic that a patentee may be its own lexicographer, and thus may use terms in a manner different from that used in the industry or its ordinary meaning. *Hormone Research Foundation, Inc. v. Genentech*, 902 F.2d 1558, 1562, 15 U.S.P.Q.2d 1039 1043 (Fed.Cir. 1990). In this connection, the '774 patent specifically defines microbubbles and microballoons differently:

> microbubbles only have an immaterial or evanescent envelope, i.e. they are only surrounded by a wall of liquid whose surface tension is being modified by the presence of a surfactant, ... microballoons or microcapsules have a tangible envelope made of substantive material, e.g. a polymeric membrane with definite mechanical strength.

'774 patent, col. 2, lines 21-27. Each of the claims in issue further define these terms. Such distinction between the '774 patent's microbubbles (referred to as "stabilized microbubbles" herein since the '774 teaches that these microbubbles may be stabilized by a layer of phospholipid surfactant) and microballoons give rise to a host of different properties. For example, stabilized microbubbles are more elastic and more easily eliminated from the body than microballoons. Wheatley Declaration, ¶ 16.

Applicants have not used the terms microbubbles, microballoons, microparticles, microspheres, gas bubbles, microcapsules, or gas filled liposomes interchangeably and

indistinguishably from one another. If art references use these or similar terms, the references must be examined to determine how the terms are being used. In fact, for each reference asserted by the Examiner, Applicants will demonstrate herein how these terms are used, if at all, in the reference. Thus, a broad statement that the terms are interchangeable and indistinguishable is technically incorrect and contrary to the express teachings of the ultrasound imaging art, including the teachings of the '774 patent. Accordingly, Applicants respectfully request that the administrative notice to that effect be withdrawn.

B. Effective Priority Date

The Examiner stated that the effective priority date for the '774 reissue claims is January 23, 1992 because the priority documents submitted by the Applicants do not appear to disclose the specific gases claimed in the '774 reissue claims. Each of the priority documents in issue discloses physiologically acceptable gases like freons.

Applicants respectfully traverse this determination. The term "freon" defines a general class of fluorinated carbon-containing compounds which includes a "physiologically acceptable gas comprising an organic compound containing one or more carbon atoms and fluorine. Chlorine, bromine, and hydrogen atoms also may be present." Chambers Declaration, ¶ 5. Furthermore, the gases listed in the '774 reissue claims, like other chemical classes, also share certain properties characteristic of the "freon" class. Chambers Declaration, ¶ 5. Therefore, one skilled in the art would understand "freon" to be a disclosure of CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10} as recited in the '774 reissue claims. See Chambers Declaration, ¶ 5; Wheatley Declaration, ¶ 92; Violante Declaration, ¶ 12. For example, CF_4 is known as freon 14, C_4F_8 is freon C-318, and C_2F_6 is freon 116.

Furthermore, one skilled in the art would also understand SF_6 to also be disclosed by "physiologically acceptable gases like ... freon" since SF_6, like freon, is a fluorine containing gas with similar properties. See Chambers Declaration, ¶ 5.

Therefore, Applicants respectfully submit that the effective priority date for the '774 reissue claims 1-7, 13-15, 18, 21-26, 32, 35, and 37-42 wherein the contrast agent comprises stabilized microbubbles is April 2, 1990, the filing date of Schneider's EP No. 90810262.7.

Applicants also respectfully submit that the effective priority date for the '774 reissue claims 16-17, 19-20, 27-31, 33-34, 36, and 43-48 wherein the contrast agent comprise microballoons is May 18, 1990, the filing date of Schneider's EP No. 90810367.4.

Applicants also submit that no perfection to EP 93810885.9 is needed in order to be accorded the effective filing date of the aforementioned applications.

C. Anticipation Under Section 102

Claims 1, 12-17, 32-36, 42 and 48 have been rejected under 35 U.S.C. § 102(b, e) as anticipated by Albayrak U.S. Patent No. 5,730,951 (hereinafter referred to as "Albayrak" or "'951 patent").

For the reasons set forth below, Applicants respectfully traverse these rejections. Applicants maintain that Albayrak does not disclose, teach, or suggest Applicants' claimed invention.

As an initial matter, claim 12 has been cancelled and thus is not pending in this proceeding. Furthermore, as Applicants have shown that the effective filing date for the '774 reissue claims are April 2, 1990 and May 18, 1990 respectively, Albayrak is not prior art to the '774 reissue claims since Albayrak's effective filing date of February 25, 1991 is later than either

effective filing date for the '774 reissue claims. Nevertheless, for completeness, Applicants will substantively address Albayrak below.

To anticipate a claim, a single prior art reference must disclose each and every element of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477, 44 U.S.P.Q.2d 1429, 1431 (Fed. Cir. 1997), citing *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 U.S.P.Q.2d 1565 (Fed. Cir. 1995); *Verdegall Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1501, 1503 (Fed. Cir. 1987) *cert denied,* 484 U.S. 827 (1987). A prior art reference does not anticipate a claimed invention even if the reference discloses most of or substantially the same elements as the claimed invention. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 756 F.2d 1556, 1560, 225 U.S.P.Q. 253, 256 (Fed.Cir. 1985).

At the outset, Applicants point out that the independent claims rejected under 35 U.S.C. § 102 are as follows: reissue claims 1, 13, 15-17, and 32-34.

Reissue claims 1 and 15 recite, *inter alia*, a method of making a contrast agent having resistance against collapse from pressure increases which occur upon injection into the bloodstream, said contrast agent consisting of microbubbles bounded by an evanescent gas/liquid interfacial closed surface, said method comprising forming microbubbles in the presence of a physiologically acceptable fluorine containing gas. Reissue claims 13 and 32 recite, *inter alia*, a method of making a contrast agent, consisting of microbubbles having resistance against collapse from pressure increases which occur upon injection into the bloodstream, said method comprising forming microbubbles in the presence of a physiologically acceptable fluorine containing gas, said gas being such that, under standard conditions, the pressure difference between pressures at which the bubble counts are about 75% and 25% of the original bubble count is at least 25 Torr. Reissue claims 33 and 34 recite, *inter alia*, a method of making a

contrast agent, consisting of microballoons having resistance against collapse from pressure increases which occur upon injection into the bloodstream, said method comprising forming microballoons in the presence of a physiologically acceptable fluorine containing gas, said gas being such that, under standard conditions, the pressure difference between pressures at which the bubble counts are about 75% and 25% of the original bubble count is at least 25 Torr. Reissue claims 16 and 17 recite, *inter alia*, a method of making a contrast agent having resistance against collapse from pressure increases which occur upon injection into the bloodstream, said contrast agent consisting of microballoons bounded by a material envelope, said method comprising forming microballoons in the presence of a physiologically acceptable fluorine containing gas. Albayrak does not disclose, teach or suggest any of the above recited claim limitations of the '774 independent reissue claims. Wheatley Declaration, ¶¶ 25-31; Violante Declaration, ¶¶ 7-9; Atwood Declaration, ¶¶ 7-12.

Moreover, Albayrak does not even mention the increase in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent and provides no data establishing that the disclosed agents are echogenic in vivo. Wheatley Declaration, ¶ 15.

Instead, Albayrak discloses the entrapment of gas bubbles in solid cavitate or clathrate host/guest complexes. Atwood Declaration, ¶ 7. Unlike the '774 patent's claimed stabilized microbubbles and microballoons, these host/guest complexes are crystalline and can be reduced by mechanical processes such as air jet grinding. Wheatley Declaration, ¶ 14. These host/guest complexes are also fundamentally different in structure from the '774 patent's claimed stabilized microbubbles and microballoons. Atwood Declaration, ¶¶ 9-10. Albayrak further explains that when the host/guest complexes are put into an aqueous vehicle:

> the host molecules dissolve [, and] the complexes are broken down through the release of the gas bubbles into the vehicle. The host molecules dissolved in the vehicle no longer have any complexing properties.

'954 patent, col. 2, lines 23-28. Wheatley Declaration, ¶ 26; Atwood Declaration, ¶ 8. Thus, these host/guest complexes dissolve and release guest gas bubbles which function as the contrast agent. Wheatley Declaration, ¶ 26; Atwood Declaration, ¶ 8. The stabilized microbubbles and microballoons of the Schneider '774 reissue claims do not perform this kind of "dissolve and release" mechanism. Wheatley Declaration, ¶ 27.

There is no teaching in Albayrak that these guest gas bubbles are stabilized by any layer of surfactant or surrounded by any tangible membrane. Wheatley Declaration, ¶ 28. Instead, Albayrak only discloses use of viscosity or thickening agents such as albumin which are dispersed throughout the solution and not surrounding the gas. Wheatley Declaration, ¶ 28; Atwood Declaration, ¶11. Therefore, Albayrak's contrast agents are free gas microbubbles, which are a completely different invention from the stabilized microbubbles and microballoons of the Schneider '774 reissue claims. Wheatley Declaration, ¶¶ 19-21, 28; Atwood Declaration, ¶ 11.

The Examiner's reference to administrative notice that Albayrak's albumin "would be fully expected to assemble at the air liquid interface" is not correct. Albayrak's albumin is not denatured and thus it will remain freely soluble and in solution, and will not assemble anywhere. The Examiner may be confusing this albumin with Feinstein-like denatured albumin. However, use of such denatured albumin would work counter to Albayrak's cavitate or clathrate host/guest complexes, interfering with the structure, and thus is simply not disclosed by Albayrak. Furthermore, since Albayrak uses soluble albumin as a normal excipient (e.g., viscosity agent)

which does not assemble at a gas/liquid interface, Albayrak teaches away from the stabilized microbubbles and microballoons of the '774 reissue claims.

Thus, Albayrak fails to teach each and every element of the independent Schneider '774 reissue claims 1, 13, 15-17, 32-35. Wheatley Declaration, ¶¶ 24-31; Violante Declaration, ¶¶ 7-8; Atwood Declaration, ¶¶ 9-12. The dependent claims 14, 36, 42, and 48 were also rejected by the Examiner under 35 U.S.C. § 102. For all the reasons discussed above relating to the independent claims, Applicants maintain that the dependent claims likewise are not anticipated by Albayrak.

D. Obviousness Under Section 103

Claim 1-7 and 13-48 have been rejected under 35 U.S.C. § 103 as being obvious over, Rössling et al., U.S. Patent No. 5,501,363 (hereinafter referred to as "Rössling" or the "'363 patent"); Tickner et al., U.S. Patent No. 4,276,885 (hereinafter referred to as "Tickner I" or "'885 patent"); Tickner, U.S. Patent No. 4,265,251 (hereinafter referred to as "Tickner II" or "'251 patent"); Albayrak et al., U.S. Patent No. 5,730,951 (hereinafter referred to as "Albayrak" or "'951 patent"); Illum et al., PCT No. PCT/GB91/00247 ("hereinafter referred to as "Illum" or "'247 application"); Glajch et al., U.S. Patent No. 5,147,631 (hereinafter referred to as "Glajch" or "'631 patent"); Hilmann et al., U.S. Patent No. 4,466,442 (hereinafter referred to as "Hilmann" or "'442 patent"); Swanson et al., "Enhancement Agents for Ultrasound Fundamentals," *Pharmaceuticals In Medical Imaging*, pp. 682-687 (1990) (hereinafter referred to as "Swanson") in view of Lincoff et al., "Intravitreal Longevity of Three Perfluorocarbon Gases," *Arch. Ophthalmology*, 98:1610-1611 (1980) (hereinafter referred to as "Lincoff I"); Lincoff et al., "Invitreal Expansion of Perfluorocarbon Bubbles," *Arch. Ophthalmology*, 98:1646 (1980) (hereafter referred to as "Lincoff II"); Gardner et al., "A Survey of Intraocular Gas Use in North America," *Arch. Ophthalmology*, 106:1188-1189 (1988) (hereinafter referred to as

"Gardner"); Jacobs, "Intraocular Gas Measurement Using A-Scan Ultrasound," *Current Eye Research*, 5(8):575-578 (1986) (hereinafter referred to as "Jacobs"); and "'Freon' Fluorocarbons: Properties and Applications" in DuPont Technical Bulletin G-1 (E.I. duPont de Nemours and Company, Wilmington, DE), pp. 1-10 (1987) (hereinafter referred to as "DuPont").

At the outset, it is noted that thirteen references have been asserted as the basis of the Examiner's obviousness rejection. As the courts have stated, the fact that it is necessary to cite such a large number of references is, in and of itself, indicative of non-obviousness. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 USPQ 402, 403 (7th Cir. 1961; *The Ric-Wil Company v. E.B. Kaiser Company,* 179 F.2d 401, 404, 84 USPQ 121,124 (7th Cir. 1950); *Reynolds et al. v. Whitin Machine Works*, 167 F.2d 78, 83, 76 USPQ 551, 555 (4th Cir. 1948); and *Racal-Vadic, Inc. v. Universal Data Systems*, 1980 U.S. Dist. LEXIS 15864, *81, 207 USPQ 902, 927 (N.D. Ala. 1980). Indeed, the inference that can be taken from the large reference citation is that no one reference is on point and that the Applicants have clearly accomplished what the prior art has repeatedly failed to do. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 USPQ 402, 403 (7th Cir. 1961).

The Examiner states that the '774 reissue claims are directed to suspension containing surfactants and microbubbles of poorly soluble halogenated hydrocarbon gases. As an initial matter, Applicants respectfully submit that the Examiner's characterization of the '774 reissue claims is inaccurate. A closer reading reveals that reissue claims 1-7, 13-15, 18, 21-26, 32, 35, and 37-42 are directed to contrast agents comprising microbubbles while reissue claims 16-17, 19-20, 27-31, 33-34, 36, and 43-48 are directed to contrast agents comprising microballoons. The stabilized microbubbles of the '774 patent have one or more thin layers of

amphiphilic surfactants which surround the gas at the gas/liquid interface to stabilize the microbubble (hence, the short hand term "stabilized microbubbles"). Wheatley Declaration, ¶ 15. On the other hand, the microballoons of the '774 patent have a material boundary or envelope such as a polymer membrane wall at the gas/liquid interface. Wheatley Declaration, ¶ 15.

Briefly, Rössling, Tickner I, Tickner II, Glajch, Swanson, and Hilmann are cited by the Examiner as teaching various types of gas filled microspheres. Lincoff I, Lincoff II, Gardner, and Jacobs are cited by Examiner as teaching the desirability of using small perfluorocarbon molecules *in vivo*. DuPont is cited by Examiner to confirm that the gases recited in the '774 reissue claims are freons. Applicants do not disagree that the term freon includes the gases recited in the '774 reissue claims (and thus Applicants should be entitled to its aforementioned effective filing date).

As discussed earlier, Applicants have shown that its effective filing date of the '774 reissue claims 1-7, 13-15, 18, 21-26, 32, 35, and 37-42 is April 2, 1990 and '774 reissue claims 16-17, 19-20, 27-31, 33-34, 36, and 43-48 is May 18, 1990. Therefore, since Albayrak (February 25,1991), Rössling, (February 11, 1991), Illum (September 5, 1991), and Glajch (April 30, 1991) all have effective filing dates after either of the effective filing dates for the '774 reissue claims, they are not prior art to the '774 reissue claims and cannot be considered in any 35 U.S.C. 103 determination.

However, for completeness, Applicants will substantively address each of those references below. As set forth in more detail below, the obviousness rejection should not be maintained because there is no proper combination of teachings presented which would result in

a *prima facie* case of obviousness, and even if a proper *prima facie* case were made, evidence sufficient to rebut the case is presented herein.

1. Applicants' Claims Are Not Obvious In View Of The Cited Art

A claim is invalid under 35 U.S.C. § 103 if the subject matter would have been obvious at the time of filing of the application. In determining whether a claim is obvious, the claimed invention must be considered as a whole. *See* 35 U.S.C. § 103; *Kimberly Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448, 233 USPQ 603, 609 (Fed. Cir. 1984). In making an obviousness evaluation, consideration should be given to the scope and content of the prior art, the differences between the prior art and the claimed subject matter, the level of ordinary skill in the pertinent art,[1] as well as any objective evidence of non-obviousness such as unexpected results, satisfaction of a long-felt need, failure of others, and the like. *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966); *Radix Corp. v. Samuels*, 1989 U.S. Dist. LEXIS 16627, 13 USPQ2d 1689 (D. D.C. 1989); *Lindemann Maschinenfabrik Gmbh v. American Hoist and Derrick Co.*, 730 F. 2d 1452, 221 USPQ 481 (Fed. Cir. 1984); *Orthopedic Equip. Co., Inc. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376, 217 USPQ 1281 (Fed. Cir. 1983).

Additionally, the following tenets of patent law must be adhered to in making this obviousness determination: (1) the claimed invention must be considered as a whole, (2) the references also must be considered as a whole and must suggest the desirability and thus the obviousness of the combination, (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention, and (4) "ought to be tried" is not the standard with which obviousness is determined. *Hodosh v. Block Drug Co.*, 786 F.2d

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[1] Applicants submit that at this time, it appears that the level of ordinary skill in the art applicable in the present case is that of a professional having experience in ultrasound contrast agents for imaging and the development or use of contrast agents therefor, with a graduate degree in chemistry or related sciences.

1136, 1143 n.5, 229 U.S.P.Q. 182, 187 (Fed. Cir. 1986)(citations omitted). Determination of obviousness can not be based on the hindsight combination of components selectively called from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select the particular elements, and to combine them in the way they were combined by the inventor. *ATD Corp. v. Lydall Inc.*, 48 U.S.P.Q.2d 1321, 1329 (Fed.Cir. 1998)

Thus, the patent or application being attacked may not be used as a template, guide, or instruction manual to assist in piecing together the prior art when making an obviousness determination. E.g., *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed.Cir. 1996); *In re Gorman*, 933 F.2d 982, 987, 18 U.S.P.Q.2d 1885, 1888 (Fed.Cir. 1991); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552-53, 220 U.S.P.Q. 303, 312-13 (Fed.Cir. 1983). In other words, the invention must be viewed "not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made." *Sensonics*, 81 F.3d at 1570, 38 U.S.P.Q.2d at 1554.

Applicants respectfully submit that the claims of the '774 reissue application fully distinguish over the disclosures of Rössling, Tickner I, Tickner II, Illum, Albayrak, Glajch, Swanson, and Hilmann alone or in any properly presented combination with each other and with Lincoff I, Lincoff II, Gardner, Jacobs or Dupont.

a. *Prima Facie* Obviousness Has Not Been Established

The Examiner has the initial burden under 35 U.S.C. § 103 of establishing a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 1017, 154 USPQ 173, 178

(CCPA 1967). To do so, the Examiner generally must satisfy a number of requirements. For example, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated a person of ordinary skill in the art to modify a reference or to combine references. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988); *Ex parte Skinner*, 2 USPQ2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Moreover, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of a person of ordinary skill in the art at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.,* 927 F.2d 1200, 1207, 18 USPQ2d 1016, 1022 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991). Furthermore, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Furthermore, there must be some reason, "other than hindsight gleaned from the invention itself", "in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051, 5 U.S.P.Q.2d 1434, 1438 (Fed.Cir. 1988); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551 (Fed.Cir. 1985). One cannot cannot simply pick and choose among the individual elements of the assorted prior art references "as a mosaic to recreate a facsimile of the claimed invention." *Akzo N.V. v. U.S. Intern. Trade Comm'n*, 808 F.2d 1471, 1481, 1 U.S.P.Q.2d 1241, 1246 (Fed.Cir. 1986). *Also SmithKline Diagnostics v. Helena Lab. Corp.*, 859 F.2d 878, 887, 8 U.S.P.Q.2d 1468, 1475 (Fed. Cir. 1988). A holding that the claims of the subject patent are invalid based merely upon finding similar elements in separate prior art patents would be "contrary to statute and would defeat the congressional purpose in enacting Title 35."

SmithKline Diagnostics, 859 F.2d at 887, 8 U.S.P.Q.2d at 1475; *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1577, 1 U.S.P.Q.2d 1593, 1605 (Fed.Cir. 1987). Thus, the absence of such a suggestion to combine the asserted references is dispositive in an obviousness determination. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579, 42 U.S.P.Q.2d 1378, 1383 (Fed.Cir. 1997)(emphasis supplied).

b. Rössling Teaches Microparticles Which Are Completely Different From The Stabilized Microbubbles Or Microballoons Of The '774 Reissue Claims

The Examiner states that Rössling teaches microspheres which may be filled with fluorinated gases such as sulfur hexafluoride and a low molecular weight fluorinated hydrocarbon, both of which are poorly soluble in water, for use in ultrasonic imaging. The Examiner also states that Rössling addresses the importance of finding a gas which has long duration in the blood and notes low solubility as a criteria. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use poorly soluble gases taught by Lincoff I, Lincoff II, Gardner, and Jacobs with Rössling to practice the invention of the '774 reissue claims.

Applicants respectfully traverse the Examiner's rejection. As will become clear, Applicants will first establish that the contrast agent disclosed in Rössling is completely different from the '774 patent's claimed stabilized microbubbles and microballoons. The later section of this response will then address the inapplicability of the subject matter of Lincoff I, Lincoff II, Gardner, and Jacobs references to the '774 invention.

Rössling is directed to ultrasound contrast media comprising aqueous suspensions of microparticles formulated from biodegradable polymers and containing gases and/or readily volatile liquids (*i.e.*, liquids having boiling points of less than 60°C). *See* Rössling, col. 1, ln. 65

to col. 2, ln. 6. Unlike the '774 patent's claimed stabilized microbubbles or microballoons, which are gas bubbles surrounded by surfactants present at the gas/liquid interface or a material boundary or envelope, respectively, the microparticles of Rössling are rigid, particulate structures which may be porous and are often crystalline. Gas may be adsorbed to these rigid particles and, in certain circumstances entrapped in pores; however, the gas-filled spaces are generally too small for good echogenic response. Wheatley Declaration, ¶ 51.

Not only are the Rössling microparticles different from the '774 patent's claimed stabilized microbubbles and microballoons, but Rössling itself fails to teach or suggest the specific limitations recited in the '774 reissue claims. For example, Rössling also does not teach or suggest a method for making a contrast agent which is resistant to collapse from pressure increases which result upon injection into the blood stream, and use during ultrasonic echography. Rössling does not even mention the increase in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent. Wheatley Declaration, ¶ 52. Thus, it is clear that Rössling does not teach the limitations of the '774 independent reissue claims.

Rössling also fails to teach or suggest the limitations of the Schneider dependent reissue claims. For instance, Rössling fails to disclose or suggest the use of film-forming surfactants in lamellar or laminar form to stabilize microbubbles as claimed in reissue claims 4-7 and 23-26. Rössling also fails teach or suggest that these surfactants may comprise the phospholipids recited in reissue claims 5-7 or 24-26. Similarly, Rössling fails to disclose or suggest the organic polymer microballoons of claims 27-29. Wheatley Declaration, ¶ 53.

Rössling also fails to teach or suggest dry precursors of stabilized microbubbles or microballoons, or the method of forming the recited contrast agents using such precursors

claimed in reissue claim 30. Additionally, Rössling fails to teach or suggest the methods of reissue claim 31 or the desirability of using gases meeting the ΔP limitation of reissue claims 13-14 or 32-36. Wheatley Declaration, ¶ 54.

Rössling discloses a wide variety of gases and/or volatile liquids. *See* Rössling, col. 3, ln. 42 to col. 4, ln. 21. However, Rössling does not teach anywhere that fluorinated gases are preferred. Wheatley Declaration, ¶ 55.

Rössling itself fails to provide any suggestion or incentive which would have motivated one of ordinary skill in the art to combine with the other references cited by the Examiner. A person of ordinary skill in the art would not have been motivated to make contrast agents including stabilized microbubbles or microballoons using any of the gases of the '774 reissue claims upon reading Rössling alone or in combination with any or all of the other references cited by the Examiner. Wheatley Declaration, ¶ 55; Violante Declaration, ¶ 9[2].

Accordingly, since Rössling has not been shown to teach or suggest all of the elements of the independent or dependent claims alone or when combined with any or all of the other cited references, obviousness has not been shown and the rejection under § 103 of reissue claims 1-7, and 13-48 based on Rössling should be withdrawn.

c. Tickner I's Disclosure Of Free Gas Microbubbles Dispersed In Gelatin Is Distinct From The Stabilized Microbubbles And Microballoons Of The '774 Reissue Claims

The Examiner cites Tickner I as disclosing microbubbles of fluorinated chemicals enclosed in various interfacial membranes for use in ultrasonic imaging. The Examiner also stated that Tickner I addresses the importance of finding a gas which has long duration in the

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[2] As the Wheatley and Violante Declaration and Exhibits establish, Dr. Wheatley and Dr. Violante are both experts in the field of ultrasound contrast agents, possessing all of the credentials necessary to comment on issues relating to persons of ordinary skill in the relevant art.

blood and notes low solubility as a criteria. Thus, the Examiner states that it would have been obvious to one of ordinary skill in the art to use poorly soluble gases taught by Lincoff I, Lincoff II, Gardner, Jacobs or DuPont with Tickner to practice the invention of the '774 reissue claims.

Applicants respectfully traverse the Examiner's rejection. As with Rössling, Applicants will first establish that the contrast agent disclosed in Tickner is entirely distinct from the '774 patent's claimed stabilized microbubbles and microballoons, and then address the inapplicability of the subject matter of Lincoff I, Lincoff II, Gardner, Jacobs, and DuPont references to the '774 invention in the later section of this response.

Tickner I is directed to contrast agents comprising free gas microbubbles dispersed in gelatin membranes. *See* Tickner I, col. 4, lines 6-11. Lear Declaration, ¶ 8. As consistent with the teaching of the BURP report, these gelatin membranes are warmed and dissolved in order to release free gas microbubbles which then functions as the ultrasound contrast agent. Lear Declaration, ¶ 9. The function of the gelatin structure in Tickner I is to act as a viscosity barrier to reduce the rate at which these free gas microbubbles may contact each other and coalesce. Lear Declaration, ¶¶ 11-12. These gelatin structures are also not strongly amphiphilic nor do they have the surface active properties of surfactants, and thus would not form a layer at the gas/liquid interface. Lear Declaration, ¶¶ 14-15. Thus, at the outset, Tickner's gelatin structures function in a completely different way from the microbubbles and microballoons of the '774 reissue claims where the gas is stabilized by a layer of amphiphilic surfactant or a material boundary. Lear Declaration, ¶ 19. Furthermore, free gas microbubbles, which is what serves as the contrast agent in Tickner I, are distinct from the stabilized microbubbles and microballoons of the '774 reissue claims. Wheatley Declaration, ¶¶ 19-21.

Not only is the structure of Tickner I dissimilar to that of the '774 patent, but Tickner I itself fails to teach or suggest the specific limitations recited in the '774 independent reissue claims. For example, Tickner I does not teach or suggest a method for making a contrast agent which is resistant to collapse from pressure increases which occur upon injection into the bloodstream and use during ultrasonic echography. Indeed, Tickner I does not even mention the increases in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent. Wheatley Declaration, ¶ 36. There is also no teaching in Tickner I of any of the fluorinated gas recited in the '774 reissue claims.

Tickner I also fails to teach or suggest the limitations of the Schneider dependent claims. For instance, as discussed supra, Tickner I fails to disclose or suggest the use of film-forming surfactants in lamellar or laminar form to stabilize microbubbles as claimed in claims 4-7 or 23-26, nor does Tickner teach that these surfactants may comprise the phospholipids recited in claims 5-7 and 24-26. Similarly, as explained, Tickner I fails to disclose or suggest the microballoons with an organic polymer membrane of claims 27-29. Wheatley Declaration, ¶ 37.

Additionally, Tickner I fails to teach or suggest dry precursors of stabilized microbubbles or microballoons, or the method of forming the recited contrast agents using such precursors claimed in reissue claim 30. Tickner also completely fails to teach or suggest the methods of claim 31 or the use of gases meeting the ΔP limitation of reissue claims 13-14 and 32-36. Wheatley Declaration, ¶ 38.

Tickner I fails to provide any suggestion or incentive which would have motivated one of ordinary skill in the art to combine Tickner I with the other references cited by the Examiner. A person of ordinary skill in the art would not have been motivated to make contrast agents including stabilized microbubbles or microballoons using any of the gases of the

'774 reissue claims upon reading Tickner alone or in combination with any or all of the other references cited by the Examiner. Wheatley Declaration, ¶ 39; Violante Declaration, ¶ 9.

Accordingly, since Tickner I has not been shown to teach or suggest all of the elements of the independent or dependent claims alone or when combined with any or all of the other cited references, obviousness has not been shown and the rejection under § 103 of reissue claims 1-7, and 13-48 based on Tickner I should be withdrawn.

d. Tickner II Teaches Microparticles Which Dissolve In The Bloodstream To Release Free Gas Microbubbles

The Examiner cites Tickner II as disclosing microbubbles of fluorinated chemicals enclosed in various interfacial membranes for use in ultrasonic imaging. The Examiner also stated that Tickner II addresses the importance of finding a gas which has long duration in the blood and notes low solubility as a criteria. Thus, the Examiner states that it would have been obvious to one of ordinary skill in the art to use poorly soluble gases taught by Lincoff I, Lincoff II, Gardner, Jacobs or DuPont with Tickner to practice the invention of the '774 reissue claims.

Applicants respectfully traverse the Examiner's rejection. As with Rössling and Tickner I, Applicants will first establish that the contrast agent disclosed in Tickner II is entirely distinct from the '774 patent's claimed stabilized microbubbles and microballoons, and then address the inapplicability of the subject matter of Lincoff I, Lincoff II, Gardner, Jacobs, and DuPont references to the '774 invention in the later section of this response.

Tickner II is directed to saccharide microparticle precursors which dissolve in the bloodstream to release free gas microbubbles which reflect the ultrasound signal and serve as the contrast agent:

> It follows that a plurality of ultrasonic signals are generated as a function of time as the various microbubbles are formed on

> dissolving of the various particles 26 or on dissolving of portions thereof.
>
> * * *
>
> Briefly, as each microbubble is formed by dissolving of at least part of the wall 32 to expose the hollow space 30 or as the wall 32 thins sufficiently to cause the pressurized bubble 30 to fracture it, the microbubble expands beyond its equilibrium size, and alternately expands and constructs until it finally attains substantially its equilibrium size and shape. The frequency of the signal thereby detected by the transducer 34 is a function of the pressure in the cardiovascular system 12 opposite the positioning of the transducer 34.

Tickner II, col. 4, lines 31-62. Figure 2 of Tickner II illustrates the irregular reduction of the saccharide outer wall as it dissolves to release free gas microbubbles. On the other hand, the stabilized microbubbles and microballoons of the '774 patent or reissue claims do not "dissolve" to release free gas microbubbles nor do they display any kind of irregular reduction as shown in Figure 2. Wheatley Declaration, ¶ 41. Free gas microbubbles, once again, are completely different from the stabilized microbubbles and microballoons of the '774 reissue claims. Wheatley Declaration, ¶¶ 19-21.

Furthermore, unlike the '774 patent's claimed stabilized microbubbles or microballoons, which are gas bubbles surrounded by surfactants present at the gas liquid interface or a material boundary or envelope, respectively, the Tickner II microparticles are rigid, particulate structures which may be porous and are often crystalline. Gas may be adsorbed to these rigid particles and, in certain circumstances entrapped in pores; however, the gas-filled spaces are generally too small for good echogenic response. Moreover, the gas adsorbed to or entrapped in the rigid particles cannot resonate as it does in stabilized microbubbles and microballoons. Consequently, microparticles are usually less echogenic than either stabilized microbubbles or microballoons. Wheatley Declaration, ¶ 43.

Additionally, Tickner II recommends grinding to reduce the size and number of hollow spaces of the solid precursor microparticles. '251 patent, col. 4, lines 11-14. ("Large aggregates of precursor 26 can be ground up to provide smaller particles having only one or a few hollow spaces 30, or particles 26 can be used having up to about fifty such hollow spaces 30.") However, neither of the '774 patent's claimed stabilized microbubbles nor microballoons may be subjected to grinding without destruction of their structure and echogenicity. Wheatley Declaration, ¶ 44.

Not only is the structure of the Tickner II microparticles quite dissimilar to that of the '774 patent, but Tickner II itself fails to teach or suggest the specific limitations recited in the '774 independent reissue claims. For example, Tickner II does not disclose the method of the Schneider '774 patent and reissue claims of making a contrast agent which is resistant to collapse from pressure increases which occur upon injection into the bloodstream and use during ultrasonic echography. Tickner II does not even mention the increases in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent. Wheatley Declaration, ¶ 42.

In addition, Tickner II does not teach or suggest that the fluorinated gas of the Schneider '774 reissue claims are preferred. Instead, Tickner II teaches that carbon dioxide is the preferred gas. Tickner II, col. 6, lines 62-68. Wheatley Declaration, ¶ 45.

Tickner II also fails to disclose or suggest certain of the elements of the '774 dependent reissue claims. For instance, Tickner II does not disclose or suggest the use of film forming surfactants in lamellar or laminar form to stabilize the microbubbles as claimed in Schneider '774 reissue claims 4-7 and 23-26. Wheatley Declaration, ¶ 46.

Tickner II also does not teach or suggest the method of preparing a microballoon contrast agent having resistance against pressure increases of Schneider reissue claim 31 or the desirability of using of gases meeting the ΔP limitation of Schneider '774 reissue claims 13-14 and reissue claims 32-36. Wheatley Declaration, ¶ 47.

Tickner II itself fails to provide any suggestion or incentive which would have motivated one of ordinary skill in the art to combine Tickner II with the other references cited by the Examiner. A person of ordinary skill in the art would not have been motivated to make contrast agents including stabilized microbubbles or microballoons using any of the gases of the '774 reissue claims upon reading Tickner II alone or in combination with any or all of the other references cited by the Examiner. Wheatley Declaration, ¶ 48; Violante Declaration, ¶ 9.

Accordingly, since Tickner II has not been shown to teach or suggest all of the elements of the independent or dependent claims alone or when combined with any or all of the cited references, obviousness has not been shown and the rejection under § 103 of reissue claims 1-7, and 13-43 based on Tickner II should be withdrawn.

e. The Microparticles Of Glajch Cannot Be Used To Form The Stabilized Microbubbles And Microballoons Of The '774 Reissue Claims

The Examiner cites Glajch as teaching microspheres which may be filled with fluorinated gases such as perfluoromethane and perfluoroethane for use in ultrasonic imaging. The Examiner also states that it would have been obvious to one of ordinary skill in the art to use poorly soluble gases taught by Lincoff I, Lincoff II, Gardner, and Jacobs with Glajch to practice the invention of the '774 reissue claims.

Applicants respectfully traverse the Examiner's rejection. Following the same format as above, Applicants will first establish that the contrast agent disclosed in Glajch is completely different from the '774 patent's claimed stabilized microbubbles and microballoons.

The later section of this response will then address the inapplicability of the subject matter in Lincoff I, Lincoff II, Gardner, and Jacobs references to the '774 invention.

Glajch does not teach or suggest either the stabilized microbubbles or microballoons of the '774 reissue claims. Instead, Glajch discloses contrast agents consisting of microparticles. Glajch, col. 2. lines 11-12 and 66-68 ("[t]he invention relates to ultrasound contrast agents comprising porous particles of inorganic material..."; "[t]he invention relates to ultrasound contrast agents comprising inorganic porous particles useful for ultrasound imaging of a body organ system."). Wheatley Declaration, ¶ 57.

As discussed supra, microparticles differ significantly from the stabilized microbubbles and microballoons of the Schneider reissue claims. Unlike the '774 patent's claimed stabilized microbubbles or microballoons, microparticles are rigid particulate structures. Glajch teaches that the microparticles are "porous" and that the inorganic material forming the particles may be "crystalline." Glajch, col. 2, lines 11-13 and col. 3, lines 13-16. Further, Glajch explains that, unlike the '774 patent's claimed stabilized microbubbles or microballoons, the microparticles he teaches may range in shape or morphology and may be "irregular" or "rod-like." Glajch, col. 5, lines 23-27. The gas may be absorbed to the rigid microparticles and, in certain circumstances entrapped in pores; however, the gas filled spaces are generally too small for good echogenic response. Moreover, the gas absorbed to or entrapped in the rigid particles cannot resonate as it does in stabilized microbubbles and microballoons. Consequently, microparticles are usually less echogenic than either stabilized microbubbles or microballoons. Indeed, the Glajch patent fails to provide any data or other evidence establishing that the disclosed agents are echogenic, in vivo or otherwise. See '774 patent, at col. 3, lines 45-47. Wheatley Declaration, ¶ 58.

Not only are the microparticle structures of Glajch distinct from the stabilized microbubbles and microballoons of the '774 reissue claims, but Glajch also fails to teach or suggest the specific limitations recited in the '774 reissue claims. For example, Glajch does not teach or suggest a method for making a contrast agent which is resistant to collapse from pressure increases which occur upon injection into the blood stream and use during ultrasonic echography. Glajch also does not mention the increase in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent. Wheatley Declaration, ¶ 59

Glajch also fails to disclose or suggest the limitations of any of the Schneider dependent reissue claims. For instance, Glajch does not disclose or suggest stabilized microbubbles, nor the use of film-forming surfactants in lamellar or laminar form to stabilize microbubbles as claimed in reissue claims 4-7 or 23-26. Similarly, Glajch fails to teach that these surfactants comprise the phospholipids recited in claims 5-7 or 24-26. Wheatley Declaration, ¶ 60

Moreover, as discussed supra, Glajch fails to disclose microballoons, therefore Glajch cannot teach or suggest the microballoons with organic polymer membranes of claims 27-29. Wheatley Declaration, ¶ 61.

Glajch also fails to teach or suggest dry precursors of stabilized microbubbles or microballoons. Thus, Glajch cannot teach or suggest the method of forming the recited contrast agents using the precursors recited in reissue claim 30. Additionally, Glajch fails to teach or suggest the methods of reissue claim 31 or the use of stabilized microbubbles or microballoons containing gases meeting the ΔP limitation of reissue claims 13-14 or 32-36. Indeed, as explained supra, Glajch fails to teach or suggest pressure resistance or the importance of the ΔP

limitation. Indeed, Glajch does not even teach that pressure resistance is desirable in a contrast agent. Wheatley Declaration, ¶ 62.

Moreover, although Glajch teaches that a number of gases may be used in the disclosed contrast agents, Glajch does not teach that fluorinated gases are preferred over the other disclosed gases. Wheatley Declaration, ¶ 63.

Glajch itself fails to provide any suggestion or incentive which would have motivated a person of ordinary skill in the art to combine Glajch with the other references cited by the Examiner. A person of ordinary skill in the art would not have been motivated to make contrast agents including stabilized microbubbles or microballoons using any of the gases of the '774 reissue claims upon reading Glajch alone or in combination with any or all of the other references cited by the Examiner. Wheatley Declaration, ¶ 63; Violante Declaration, ¶ 9.

Accordingly, since Glajch has not been shown to teach or suggest all of the elements of the independent or dependent claims alone or when combined with any or all of the cited reference, obviousness has not been shown and the rejection under § 103 of reissue claims 1-7, and 13-48 based on Glajch should be withdrawn.

f. Hilmann Does Not Teach Or Suggest Either The Stabilized Microbubbles Or Microballoons Of The '774 Reissue Claims

The Examiner cites Hilmann as teaching gas-filled microspheres for use in ultrasonic imaging. The Examiner also states that it would have been obvious to one of ordinary skill in the art to use poorly soluble gases taught by Lincoff I, Lincoff II, Gardner, and Jacobs with Hilmann to practice the invention of the '774 reissue claims.

Applicants respectfully traverse the Examiner's rejection. Following the same format as above, Applicants will first establish that the contrast agent disclosed in Hilmann is completely different from the '774 patent's claimed stabilized microbubbles and microballoons.

The later section of this response will then address the inapplicability of the subject matter in Lincoff I, Lincoff II, Gardner, and Jacobs references to the '774 invention.

Hilmann discloses microbubbles consisting essentially of solution containing a selected amount of tenside, viscosity raising compound, and physiologically acceptable gas. Hilmann, col. 2, lines 42-56. Experiments conducted by Dr. Michel Schneider based on Example 2 disclosed by Hilmann reveal that Hilmann's contrast agents have properties very similar to free gas microbubbles and not to the stabilized microbubbles or microballoons of the '774 reissue claims. In particular, the results of Dr. Schneider's experiments establish that Hilmann's microbubbles, like free gas microbubbles, were very large, unstable and could not result in opacification of the left ventricle. Schneider Declaration, ¶¶ 8-11. On the contrary, the microbubbles of the '774 patent were very stable, showing no significant change in bubble size for over an extended period of time. Schneider Declaration, ¶ 12.

Furthermore, not only are there structural differences between the contrast agents themselves, but Hilmann also does not teach or suggest the specific limitations recited in the '774 independent reissue claims. For example, Hilmann does not disclose the method of the Schneider '774 patent and reissue claims of making a contrast agent which is resistant to collapse from pressure increases which occur upon injection into the bloodstream and use during ultrasonic echography. Hilmann does not mention the increases in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent. Wheatley Declaration, ¶ 66.

Hilmann also fails to disclose or suggest certain of the elements of the dependent Schneider '774 reissue claims. For instance, Hilmann does not disclose or suggest the use of any fluorinated gases, including the use of specific fluorinated gases of Schneider reissue claims 37-

48. Hilmann also fails to disclose or suggest the use of film-forming surfactants in lamellar or laminar form to stabilize the microbubbles as claimed in Schneider '774 reissue claims 4-7 or 23-26. In fact, the Hilmann preferred tensides (polyoxyethylene fatty acid stearates and polyoxypropylene polymers such as Pluronic) are not film forming. Hilmann states that the tensides are not used to stabilize the microbubbles, rather they are used to control the size of the bubbles produced. '442 patent, col. 9, lines 45-49. The reported lack of stability of the Hilmann preparations and their inability to provide images of the left ventricle indicates that the Hilmann preparations are not stabilized by a film forming surfactant in lamellar or laminar form. Hilmann also fails to disclose or suggest microballoons with an organic polymer membrane of Schneider '774 patent reissue claims 27-29. Wheatley Declaration, ¶ 67.

Hilmann fails to teach or suggest the method of preparing a microballoon contrast agent having resistance against pressure increases of Schneider reissue claim 31 or the desirability of using gases meeting the ΔP limitations of Schneider '774 reissue claims 13-14 or 32-36. Wheatley Declaration, ¶ 68.

Hilmann itself fails to provide any suggestion or incentive which would have motivated a person of ordinary skill in the art to combine Hilmann with the other references cited by the Examiner. A person of ordinary skill in the art would not have been motivated to make contrast agents including stabilized microbubbles or microballoons using any of the gases of the '774 reissue claims upon reading Hilmann alone or in combination with any or all of the other references cited by the Examiner. Wheatley Declaration, ¶ 69; Violante Declaration, ¶ 9.

Accordingly, since Hilmann has not been shown to teach or suggest all of the elements of the independent or dependent claims alone or when combined any or all of the other

cited references, obviousness has not been shown and the rejection under § 103 of reissue claims 1-7, and 13-48 based on Hilmann should be withdrawn.

g. Swanson Does Not Teach Or Suggest Either The Stabilized Microbubbles Or Microballoons Of The '774 Reissue Claims

The Examiner asserted that Swanson particularly teaches perfluorocarbons which are gases at body temperature. Applicants respectfully traverse the Examiner's rejection in view of Swanson. Applicants maintain that Swanson, alone or in any combination with the other references cited by the Examiner, does not teach or suggest either the stabilized microbubbles or microballoons of reissue claims 1-7 or 13-48.

Applicants suggest that the Examiner mischaracterizes what is found in Swanson. At the outset Applicants point out that Swanson is essentially a review article discussing a variety of enhancement agents for ultrasound. Contrary to the Examiner's assertion, Swanson does not particularly teach any of Applicants' specifically claimed fluorinated gases. Swanson merely states that fluorocarbons are an example of an agent which reacts *in vivo* to form bubbles. Swanson specifically mentions perfluorodecalin and perfluorotripropylamine, both of which are liquid, but does not suggest that even these fluorocarbons are preferred. Wheatley Declaration, ¶ 85. In fact, Swanson suggests that for echogenic opacification of the heart, dilute hydrogen peroxide should be used and that a better contrast is achieved if it is mixed with a small amount of blood just prior to intravenous injection. Swanson goes on to state that perfluorocarbons (generically) can be used for echogenic enhancement of the liver and spleen. Swanson article at pp. 685-86. Swanson does not even mention echogenic enhancement of the heart using perfluorocarbons. Thus, it is implicit in Swanson that contrast agents comprising substances other than perfluorocarbons (i.e. hydrogen peroxide) are more suitable for those areas of the body which may be subject to greater pressure changes.

Moreover, Swanson does not teach or suggest a method for making a contrast agent which is resistant to collapse from pressure increases which result upon injection into the blood stream or the use of such agents during ultrasonic echography. Swanson does not even mention the increase in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent. Wheatley Declaration, ¶ 82.

Swanson also fails to teach or suggest the limitations of the Schneider dependent claims. For instance, Swanson fails to disclose or suggest the use of film-forming surfactants in lamellar or laminar form to stabilize microbubbles as claimed in reissue claims 4-7 and 23-26, nor does Swanson teach that these surfactants may comprise the phospholipids recited in reissue claims 5-7 and 24-26. Similarly, Swanson fails to disclose or suggest the organic polymer microballoons of claims 27-29. Wheatley Declaration, ¶ 83.

Swanson also fails to teach or suggest dry precursors of stabilized microbubbles or microballoons, or the method of forming the contrast agents using the precursors recited in reissue claim 30. Additionally, Swanson fails to teach or suggest the recited method of reissue claim 31 or the desirability of using gases meeting the ΔP limitation of reissue claims 13-14 and 32-36. Wheatley Declaration, ¶ 84.

Accordingly, a person of ordinary skill in the art would not have been motivated to make a contrast agent including stabilized microbubbles or microballoons recited in claims 1-7 and 13-48 using any of the gases of the Schneider '774 reissue claims upon reading Swanson alone or in combination with any or all of the other art mentioned in this declaration.

h. Albayrak Free Gas Microbubbles Do Not Teach Or Suggest Either The Stabilized Microbubbles Or Microballoons Of The '774 Reissue Claims

The Examiner cites Albayrak as teaching microspheres which may be filled with poorly soluble gases for use in ultrasonic imaging in a solution containing albumin. The Examiner took administrative notice that albumin would assemble at the gas/liquid interface. The Examiner also states that it would have been obvious to one of ordinary skill in the art to use poorly soluble gases taught by Lincoff I, Lincoff II, Gardner, and Jacobs with Glajch to practice the invention of the '774 reissue claims.

Applicants respectfully traverse the Examiner's rejection. Once again, Applicants will first establish that the contrast agent disclosed in Albayrak is completely different from the '774 patent's claimed stabilized microbubbles and microballoons. The later section of this response will then address the inapplicability of the subject matter in Lincoff I, Lincoff II, Gardner, and Jacobs references to the '774 invention.

As discussed above, Albayrak discloses the entrapment of gas bubbles in solid cavitate or clathrate host/guest complexes. Atwood Declaration, ¶ 7. Unlike the '774 stabilized microbubbles and microballoons, these host/guest complexes are crystalline and can be reduced by mechanical processes such as air jet grinding. Wheatley Declaration, ¶ 14. These host/guest complexes are also fundamentally different in structure from the '774 stabilized microbubbles and microballoons. Atwood Declaration, ¶¶ 9-10. Albayrak further explains that when the host/guest complexes are put into an aqueous vehicle:

> the host molecules dissolve [, and] the complexes are broken down through the release of the gas bubbles into the vehicle. The host molecules dissolved in the vehicle no longer have any complexing properties.

'954 patent, col. 2, lines 23-28. Wheatley Declaration, ¶ 26; Atwood Declaration, ¶ 8. Thus, these host/guest complexes dissolve and release guest gas bubbles which function as the contrast agent. Wheatley Declaration, ¶ 26; Atwood Declaration, ¶ 8. The microbubbles and

microballoons of the Schneider '774 reissue claims do not perform this kind of "dissolve and release" mechanism. Wheatley Declaration, ¶ 27.

There is no teaching in Albayrak that these guest gas bubbles are stabilized by any layer of surfactants or surrounded by any tangible membrane. Wheatley Declaration, ¶ 28. Instead, Albayrak only discloses use of viscosity or thickening agents such as albumin which are dispersed throughout the solution and not surrounding the gas. Wheatley Declaration, ¶ 28; Atwood Declaration, ¶ 11. Therefore, Albayrak's contrast agents are free gas microbubbles, which are completely different from the microbubbles and microballoons of the Schneider '774 reissue claims. Wheatley Declaration, ¶¶ 19-21, 28; Atwood Declaration, ¶ 11.

The Examiner's reference to administrative notice that Albayrak's albumin "would be fully expected to assemble at the air liquid interface" is not correct. Albayrak's albumin is not denatured and thus it will remain freely soluble and in solution, and will not assemble anywhere. The Examiner may be confusing this albumin with Feinstein-like denatured albumin. However, use of such denatured albumin would work counter to Albayrak's cavitate or clathrate host/guest complexes, interfering with the structure, and thus is simply not disclosed by Albayrak. Furthermore, since Albayrak uses soluble albumin as a normal excipient (e.g., viscosity agent) which does not assemble at a gas/liquid interface, Albayrak teaches away from the stabilized microbubbles and microballoons of the '774 reissue claims.

In addition to disclosing a totally different contrast agent structure from the stabilized microbubbles and microballoons of the '774 reissue claims, Albayrak does not even mention the increase in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent and provides no data establishing that the disclosed agents are echogenic in vivo. Wheatley Declaration, ¶ 15.

Albayrak also fails to teach or suggest the limitations of the Schneider dependent reissue claims. For instance, Albayrak fails to disclose or suggest the use of film forming surfactants in lamellar or laminar form to stabilize the microbubbles as claimed in reissue claims 4-7 or 23-26, nor does Albayrak teach that the surfactants may comprise the phospholipids recited in reissue claims 5-7 and 24-26. Similarly, Albayrak fails to disclose or suggest the organic polymer microballoons of claims 27-29. Wheatley Declaration, ¶ 29.

Albayrak also fails to teach or suggest the dry precursors of stabilized microbubbles or microballoons, or the method of forming the recited contrast agents using such precursors claimed in reissue claim 30. Additionally, Albayrak fails to teach or suggest the methods of reissue claim 31 or the desirability of using gases meeting the ΔP limitation of reissue claims 13-14 and 32-36. Wheatley Declaration, ¶ 30.

Furthermore, although Albayrak discloses a list of over thirty potential "guest" gases, Albayrak does not teach that fluorinated gases are preferred over the other guest gases. '954 patent, col. 2, lines 3-12.

Albayrak itself fails to provide any suggestion or incentive which would have motivated a person of ordinary skill in the art to combine Albayrak with the other references cited by the Examiner. A person of ordinary skill in the art would not have been motivated to make contrast agents including stabilized microbubbles or microballoons using any of the gases of the '774 reissue claims upon reading Albayrak alone or in combination with any or all of the other references cited by the Examiner. Wheatley Declaration, ¶ 32; Violante Declaration, ¶ 9.

Accordingly, since Albayrak has not been shown to teach or suggest all of the elements of the independent or dependent claims alone or when combined with any or all of the

other cited references, obviousness has not been shown and the rejection under § 103 of reissue claims 1-7, and 13-48 based on Albayrak should be withdrawn.

i. Illum Does Not Teach Or Suggest Either The Stabilized Microbubbles Or The Microballoons Of '774 Reissue Claims 1-7 And 13-48

The Examiner asserted that Illum teaches the formation of microbubbles using poorly soluble volatile gases and that the gas inside the microbubbles would be a mixture of air and the volatile gas. Applicants respectfully traverse the Examiner's rejection and maintains that Illum alone or in combination with any or all of the other references cited by the Examiner does not teach or suggest the stabilized microbubbles or microballoons recited in claims 1-7 and 13-48.

Applicants point out, contrary to the Examiner's assertions, that Illum is directed toward multi-chambered hollow microcapsules. In addition, Illum states that "[t]he core ... is preferably a water-immiscible oil and is preferably also relatively volatile so that it can be evaporated after the microcapsules have been formed, in other words during or after the hardening of the wall. This is what is meant by 'relatively volatile'". Illum, p. 3. Illum further states that the preferred boiling point for the water-immiscible oil is 50-80° C, well above the body temperature of all mammals. Thus, each of Illum's preferred water-immiscible oils are liquid at body temperature (i.e. 37°C). Further, Illum does not refer to any fluorinated gas recited in the '774 reissue claims.

Moreover, unlike the '774 patent's claimed stabilized microbubbles or microballoons, which are gas bubbles surrounded by surfactants present at the gas liquid interface or a material boundary or envelope, respectively, Illum's "microcapsules" are particulate structures which may be porous. In fact, Illum teaches that as its preferred product "microcapsules" have multiple gas-filled chambers. Illum, p. 3 ("More than one core can be

provided in each microcapsule."), pp. 5-6 ("At least in the case of the double emulsion methods, a multi-chamber microcapsule results, resembling a honeycomb or the type of confectionery sold in the UK under the registered trademark 'Malteser'. This is a preferred product. There may be from two to several hundred chambers in each microcapsule, preferably at least 10....The air-filled microcapsules themselves (especially the multi-chamber capsules) and their uses, particularly as echogenic materials in ultrasound procedures form further aspects of the invention.") The fact that these "microcapsules" may be multi-chambered clearly demonstrates that Illum's microcapsules are completely different from Schneider's stabilized microbubbles and microballoons, neither of which can have multiple-chambers. Wheatley Declaration, ¶ 72.

Additionally, gas may be adsorbed to these rigid "microcapsules" and in certain circumstances entrapped in pores. However, the gas-filled spaces are generally too small for good echogenic response, which explains why Illum preferred multi-chambered "microcapsules". Moreover, the gas adsorbed to or entrapped in the rigid particles cannot resonate as it does in stabilized microbubbles and microballoons. Consequently, these "microcapsules" are usually less echogenic than either stabilized microbubbles or microballoons. Wheatley Declaration, ¶ 73.

Furthermore, Illum teaches that these chambers in the "microcapsules" are formed by removing the liquid or solid core. Illum, p. 1 ("One aspect of the invention provides a process for preparing gas-containing microcapsules comprising forming water-dispersible (preferably proteinaceous) microcapsules having a liquid or solid core and removing at least some of the said liquid or solid to create a microcapsule containing a gas."), p. 3 ("the core in the process of the present invention is preferably a water-immisible oil and is preferably also relatively volatile so that it can be evaporated after the microcapsules have been formed....A solid core, such as

ammonium carbonate, may be used, followed by sublimation or removal with a solvent".) High speed stirring (i.e., 800 to 6000 rpm) is needed to effect such removal. Illum, examples, 1-7. Unlike these "microcapsules", Schneider's claimed stabilized microbubbles and microballoons do not have a liquid or solid "core" that needs to be removed by high speed stirring. Wheatley Declaration, ¶ 74.

Illum also does not teach or suggest a method for making a contrast agent which is resistant to collapse from pressure increases which result upon injection into the blood stream or the use of such agent during ultrasonic echography. Illum does not even mention the increase in pressure associated with injection into the bloodstream and contrast echography or the desirability of pressure resistance in a contrast agent. Wheatley Declaration, ¶ 75.

Illum also fails to teach or suggest the limitations of the Schneider dependent claims. For instance, Illum fails to disclose or suggest the use of film-forming surfactants in lamellar or laminar form to stabilize microbubbles as recited in reissue claims 4-7 and 23-26, nor does Illum teach that these surfactants may comprise the phospholipids recited in reissue claims 5-7 and 24-26. Similarly, Illum fails to disclose or suggest the organic polymer microballoons of claims 27-29. Wheatley Declaration, ¶ 76.

Illum also fails to teach or suggest dry precursors of stabilized microbubbles or microballoons, or the method of forming the contrast agents using such precursors recited in reissue claim 30. Additionally, Illum fails to teach or suggest the methods of reissue claim 31 or the desirability of using gases meeting the ΔP limitation of reissue claims 13-14 or 32-36. Wheatley Declaration, ¶ 77.

Accordingly, Applicants maintain that a person of ordinary skill in the art would not have been motivated to make a contrast agent including stabilized microbubbles or

microballoons using any of the gases of the Schneider '774 reissue claims upon reading Illum alone or in combination with any or all of the references cited by the Examiner. Wheatley Declaration, ¶ 78.

j. Lincoff I, Lincoff II, Gardner, and Jacobs Do Not Teach Or Suggest Either The Stabilized Microbubbles Or The Microballoons Of '774 Reissue Claims 1-7 and 13-48

Applicants maintain that Lincoff I, Lincoff II, Gardner and Jacobs (the Ocular Documents) do not teach or suggest either the stabilized microbubbles or the microballoons of '774 reissue claims 1-7 and 13-48. The Ocular Documents are all directed to the use of gases as intraocular tamponades for the treatment of retinal tears or detachments. Applicants' claims distinguish over the Ocular Documents in that the Ocular Documents completely fail to disclose or suggest the '774 patent's claimed stabilized microbubbles or microballoons. The methods disclosed in the Ocular Documents involve the use of gases in the eye. Clearly, the use of free gas alone without any surfactants or material boundary can in no way suggest Applicants' claimed stabilized microbubbles or microballoons. Wheatley Declaration, ¶¶ 88-90.

Moreover, the methods described in the Ocular Documents involve the use of a large, solitary gas bubble whose diameter is limited only by the internal diameter of the eye. Applicants' claims, on the other hand, recite microvesicles which are either microballoons or microbubbles.[3] Clearly one concerned with the development of contrast agents composed of a profusion of tiny gas filled microbubbles or microballoons would not look to the Ocular Documents which disclose the use of a single, large gas bubble. Wheatley Declaration, ¶ 88.

Lincoff I and II teach that preferred gases are those which expand within the vitreal cavity to ensure contact of the retina with the posterior surface of the eye. This represents

[3] The '774 Patent teaches that the desired size range for microbubbles or microballoons is 1 to 10 microns.

a teaching away from the use of the fluorinated gases used in contrast agents for ultrasound imaging as described and claimed in the '744 reissue application. Specifically, the use of gases which expand *in vivo* would suggest the possibility of an embolism in the bloodstream. Accordingly, a person of ordinary skill in the art would be led away from the use of fluorinated gases based on the teachings of the Ocular Documents. Wheatley Declaration, ¶ 90.

Moreover, the Ocular Documents are neither in Applicants' field of endeavor, nor are they reasonably pertinent to the problem with which Applicants are concerned, namely contrast enhancement. Accordingly, one of ordinary skill in the art of contrast agents would never have even encountered the Ocular Documents or, if encountered, have any motivation to read them. Clearly, a person of ordinary skill in the art would not look to art in the field of ophthalmology to address a problem in the ultrasound imaging field. Wheatley Declaration, ¶ 88.

The Examiner asserted that Jacobs serves as a "bridge" between the art of ultrasonic imaging and the Lincoff and Gardner references. *See* Office Action, p. 5. This is a conclusory statement which is incorrect as a matter of fact and improper as a matter of law. As discussed in detail above, Jacobs (as well as the Lincoff I and II and Gardner documents) is in the field of ocular surgery. This is completely different and unrelated to the field of Applicants' endeavor, namely, the development of contrast agents for ultrasound imaging. Jacobs is irrelevant to the problems with which one of ordinary skill in the art is faced in ultrasound imaging. Accordingly, a person of ordinary skill in the art would have had no reason to consider Jacobs when trying to solve these problems. Wheatley Declaration, ¶ 90.

Accordingly, a person of ordinary skill in the art would not have been motivated to make a contrast agent including stabilized microbubbles or microballoons recited in claims 1-

7 and 13-48 using any of the gases of the Schneider '774 reissue claims upon reading the Ocular Documents alone or in combination with any or all of the other references cited by the Examiner.

k. The Dupont Technical Bulletin Does Not Teach Or Suggest Either The Stabilized Microbubbles Or The Microballoons Of '774 Reissue Claims 1-7 and 13-48

The Examiner stated that the Dupont Technical Bulletin teaches that fluorinated molecules are a well known and explicitly exemplified sub-group of the compounds encompassed by the term freon. While Applicants agrees with the Examiner that this technical bulletin confirms that the term "freon" includes the gases of the Schneider '774 reissue claims, there is no teaching or suggestion in this bulletin that freon gases may be used in an ultrasound contrast agent, especially with a use that is injected. Wheatley Declaration, ¶ 92.

Accordingly one of ordinary skill in the art would not have been motivated to make a contrast agent including stabilized microbubbles or microballoons using any of the gases of the Schneider '774 reissue claims upon reading the Dupont Technical Bulletin in combination with any or all of the other references cited by the Examiner. Wheatley Declaration, ¶ 93.

l. There Is No Motivation To Combine Any Or All Of The Cited References To Practice The Invention Of The '774 Reissue Claims

Each of the referenced cited by the Examiner is directed to different subject matter than Applicants' invention and they do not provide motivation to combine their disparate teachings to produce the Applicants' invention.

At the outset, the Examiner does not provide any evidence of any motivation to combine any of the references cited. Instead, the Examiner only states, "One of ordinary skill would have been motivated to particularly select poorly soluble molecules from among the possible gases to be used in each of Rössling, et al, Tickner '251, Tickner et al. '885, Glajch et al., Swanson and Albayrak et al. because Lincoff et al., Lincoff et al., Gardner et al. and Jacobs

teach the desirability of using poorly soluble gases *in vivo* ultrasonic applications." September 29, 1999 Office Action, p. 3. Such statement is nothing more than a conclusory statement which is insufficient to support an assertion that the prequisite motivation exists for a finding of obviousness under 35 U.S.C. § 103. Even if it were true, the references still do not provide Applicants' stabilized microbubble and microballoons in combination with the "poorly soluble gases."

Nevertheless, for completeness, Applicants establish below that the references cited by the Examiner do not provide any motivation or suggestion to be combined to practice Applicants' claimed invention, especially since each reference teaches as its preferred embodiment a completely separate invention from the '774 patent's claimed stabilized microbubbles and microballoons.

Rössling teaches the use of microparticles. Rössling, col. 1, line 65 to col. 2, line 6. These microparticles, unlike the '774 patent's claimed stabilized microbubbles and microballoons, are rigid, particulate structures which may be porous and crystalline. Wheatley Declaration, ¶ 51. Rössling does not teach anywhere that fluorinated gases are preferred. Wheatley Declaration, ¶ 55. Thus, Rössling does not provide any suggestion or motivation to be combined with any or all of the other cited references in order to produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration, ¶ 55.

Tickner I discloses free gas microbubbles dispersed in gelatin structures which dissolve to release free gas microbubbles as the contrast agent. Tickner I, col. 4, lines 6-11. Lear Declaration, ¶ 8. Tickner I's free gas microbubbles, which do not have any layer of surfactants or material boundary surrounding the gas, is contrary to the '774 patent's claimed stabilized microbubbles and microballoons which utilizes a layer of amphiphilic surfactant or

material boundary at the gas/liquid interface and do not "dissolve" to release free gas microbubbles. Lear Declaration, ¶ 19; Wheatley Declaration, ¶¶ 19-21. Tickner I does not mention anywhere the fluorinated gases recited in the '774 reissue claims. Thus, Tickner I cannot provide any suggestion or motivation to be combined with any or all of the other cited references to produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration, ¶ 39.

Tickner II teaches microparticles which dissolve to release free gas microbubbles as the contrast agent. Tickner II, col. 4, lines 31-62. These microparticles, unlike the '774 patent's claimed stabilized microbubbles and microballoons, are rigid, particulate structures which may be porous, crystalline, and grinded. Wheatley Declaration, ¶¶ 43-44. Tickner II's free gas microbubbles, which do not have any layer of surfactants or material boundary surrounding the gas, is contradictory to the '774 patent's claimed stabilized microbubbles and microballoons which employ a layer of amphiphilic surfactant or material boundary at the gas/liquid interface and do not "dissolve" to release free gas microbubbles. Wheatley Declaration, ¶¶ 41, 19-21. Tickner II does not teach anywhere that the fluorinated gas of the '774 reissue claims are preferred, instead teaching that carbon dioxide is the preferred gas. Tickner II, col. 6, lines 62-68. Wheatley Declaration, ¶ 45. Thus, Tickner II does not offer any suggestion or motivation to be combined with any or all of the other cited references produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration, ¶ 48.

Glajch discloses the use of microparticles. Glajch, col. 2, lines 11-12 and 66-68. These microparticles, unlike the '774 patent's claimed stabilized microbubbles and microballoons, are rigid, particulate structures which may be porous and crystalline. Wheatley Declaration, ¶ 58. Glajch does not teach anywhere that fluorinated gases are preferred.

Wheatley Declaration, ¶ 63. Thus, Glajch fails to provide any suggestion or motivation to be combined with any or all of the other cited references to produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration, ¶ 63.

Hilmann teaches microbubbles which behave very similarly to free gas microbubbles and vastly different from the '774 patent's claimed stabilized microbubbles and microballoons. Schneider Declaration, ¶¶ 8-11. Hilmann does not disclose any of the fluorinated gases of the '774 reissue claims. Wheatley Declaration, ¶ 67. Therefore, Hilmann cannot provide any suggestion or motivation for combining it with any or all of the other cited references to produce the '774 patent's claimed stabilized microbubbles and microballoons.

Swanson only mentions the use of liquid fluorocarbons as an agent which reacts to form bubbles. Wheatley Declaration, ¶ 85. Swanson does not suggest anywhere that the fluorinated gases of the '774 reissue claims are preferred. Wheatley Declaration, ¶ 85. Hence, Swanson does not provide any suggestion or motivation for combining it with any or all of the other cited references produce the '774 patents' claimed stabilized microbubbles and microballoons. Wheatley Declaration ¶ 86.

Albayrak teaches solid cavitate or clathrate host/guest complexes which dissolve to release free gas microbubbles as its contrast agent. Atwood Declaration, ¶ 8; Wheatley Declaration, ¶26. Albayrak's free gas microbubbles, which do not have any layer of surfactants or material boundary surrounding the gas, is contradictory to the '774 patent's claimed stabilized microbubbles and microballoons which employ a layer of amphiphilic surfactant or material boundary at the gas/liquid interface and do not "dissolve" to release free gas microbubbles. Wheatley Declaration, ¶¶ 27-28, 19-21; Atwood Declaration, ¶ 11. Albayrak does not teach that fluorinated gases are preferred. Thus, Albayrak does not provide any motivation or suggestion to

combine it with any or all of the other cited references to produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration ¶ 32.

Illum discloses multi-chambered hollow microcapsules. These microcapsules, unlike the '774 patent's claimed stabilized microbubbles and microballoons, are rigid, particulate structures which may be porous and preferably have multiple gas-filled chambers. Wheatley Declaration, ¶ 72. Illum does not refer to any fluorinated gas recited in the '774 reissue claims. Therefore, Illum fails to provide any motivation or suggestion to be combined with any or all of the other cited references to produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration, ¶ 78.

The Ocular Documents (Lincoff I, Lincoff II, Gardner, and Jacobs) only disclose the use of expanding gases in the treatment of the eye. Such property is contrary to what is needed for ultrasound contrast agents, and thus, the Ocular Documents do not provide any motivation or suggestion for one to combine it with any or all of the other cited references to produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration, ¶¶ 88-90.

There is nothing in the DuPont reference which suggests that freon can be used as an ultrasound contrast agent, especially for use that is injected. Thus, DuPont does not suggest or motivate one to combine it with any or all of the other cited references to produce the '774 patent's claimed stabilized microbubbles and microballoons. Wheatley Declaration, ¶ 93.

As shown above, none of the cited references provide any suggestion or motivation for one to combine any or all of them together to produce the '774 patent's claimed stabilized microbubbles and microballoons. The absence of such motivation to combine these asserted references is dispositive in an obviousness determination. *Gambra Lundia AB*, 42

U.S.P.Q.2d at 1383. Merely picking and choosing among the individual elements of the various references or using hindsight to piece them together, which are the only two methods possible to combine these references, is prohibited and contrary to law. *Akzo N.V.*, 1 U.S.P.Q.2d at 1246; *SmithKline Diagnostics*, 8 U.S.P.Q.2d at 1475.

Even if there were motivation to combine any of the cited references, there is no combination which would result in the Applicants' invention. None of these references teach or suggest the stabilized microbubbles or the microballoons of the '774 reissue claims 1-7 and 13-48. For example, none of these references teach or suggest a method for making an ultrasound contrast agent having resistance against collapse from pressure increases when used in ultrasonic echography. Furthermore, these references do not even mention or discuss the pressure increases which occur when injecting the contrast agent into a bloodstream and the relative importance of having resistance to such pressure increases. Violante Declaration, ¶ 7.

At best, assuming arguendo there is a motivation to combine the references, such a combination could only product solid microparticles, solid cavitate or clathrates, rigid microcapsules, or free gas microbubbles with gases. None of this subject matter falls within the claims in issue.

In addition, these references, taken alone or in any combination, fail to teach or suggest all of the elements recited in any of the '774 dependent reissue claims. For example, with respect to the '774 stabilized microbubble reissue claims, there is no teaching or suggestion in any of these references of the use of film-forming surfactants in lamellar or laminar form (reissue claims 4-7, 23-26), phospholipid surfactants (reissue claims 5-7, 24-26), or specific pressure limitation (reissue claims 13-14 and 32-36). Similarly, with respect to the '774 microballoon reissue claims, there is no teaching or suggestion in any of these references of the

use of organic polymer membrane (reissue claims 27-29), dry precursors (reissue claim 30), or flushing (reissue claim 31). Violante Declaration, ¶ 8.

With those elements missing from each of the aforementioned references, a person of ordinary skill in the art would not have been motivated to use any combination or all of them to form the stabilized microbubbles or microballoons of the '774 reissue claims 1-7 and 13-48. Violante Declaration, ¶ 9.

Moreover, none of the contrast agent references Rössling, Tickner I, Tickner II, Albayrak, Illum, Glajch, Hilmann, and Swanson (collectively, the "Contrast Agent References") teach or suggest a preference for using fluorinated gases. Thus, a person of ordinary skill in the art would not have been motivated to use any combination or all of the asserted references to form the stabilized microbubbles or microballoons of the '774 reissue claims with the gases recited in those claims. Violante Declaration, ¶ 10. In fact, they would be led to the references' teachings, including their preferred embodiments, which all teach away from Applicants' claims.

Furthermore, because a basic premise of the Ocular Documents is the expanding properties of the fluorinated gases, a premise contrary to the property desired in ultrasound contrast agents, a person of ordinary skill in the art would not have been motivated to use those references with any of the other references cited. Violante Declaration, ¶ 11.

As there is no combination of cited references which may be used to practice Applicants' invention in the '774 reissue claims 1-7 and 13-48, withdrawal of the 35 U.S.C. § 103 rejection is respectfully requested.

2. Objective Considerations of Non-Obviousness Further Confirm The Patentability of Applicants' Claims

In addition to the foregoing, Applicants submit herewith objective evidence of non-obviousness -- the so-called secondary considerations of non-obviousness. *Graham v. John*

Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). When objective considerations are presented, they must be considered by the examiner. *In re Sernaker*, 702 F.2d 989, 996, 217 USPQ 1, 7 (Fed. Cir. 1983). Indeed, objective considerations may be the most probative indicia of non-obviousness. *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556, 225 USPQ 26, 32 (Fed. Cir. 1985); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983). Consequently, to further distinguish Applicants' invention from the references cited by the Examiner, Applicants submit the following evidence of non-obviousness: (i) unexpected results; (ii) long felt need; and (iii) failure of others.

a. Unexpected Results

It is well-settled that evidence of non-obvious or unexpected advantageous properties can be presented to rebut a *prima facie* case of obviousness. *In re Chupp*, 816 F.2d 643, 645, 2 USPQ2d 1437, 1439 (1987). Moreover, evidence that a compound is unexpectedly superior in just one of a spectrum of common properties is enough to rebut a *prima facie* case of obviousness. *In re Ackerman*, 444 F.2d 1172, 1176, 170 USPQ 340, 343 (CCPA 1971). Unexpected results are established when an applicant or Applicants demonstrates substantially improved results, states that the results were unexpected, and there is no evidence to suggest that the results are expected. *In re Soni*, 54 F.3d 746, 751, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).

Applicants submit herewith evidence which demonstrates that the '774 patent's claimed stabilized gas filled microbubbles and microballoons of the present invention perform unexpectedly and significantly better as contrast agents as compared to the gas filled microspheres of the prior art. In this regard, Applicants submits herewith the Declaration of Dr. Schneider (hereinafter referred to as the "Schneider Declaration").

As the Schneider Declaration indicates, a representative sample from the '774 patent was prepared and tested. Specifically, Example 4 of the parent application to the '774

patent, PCT/EP91/00620 (referred to in the '774 patent col. 4, lines 35-36 as disclosing the preferred microbubbles to be used for the '774 patent) was followed in all respects except C_4F_{10} was used as the gas instead of air. This type of sample is described in the specification of the '774 patent (e.g., col. 4, lines 35-36 discloses this type of phospholipid stabilized microbubble and col. 7, lines 65-68 and original claim 3, which was filed with the application, discloses the C_4F_{10} gas. See also Examples 4-6 of the '774 patent which discloses similar contrast agents). Schneider Declaration, ¶ 3.

The sample was analyzed with a Leica Quantimet which indicated that the suspension contained between 10^7 and 10^8 bubbles per ml. The bubbles had a mean diameter of 4-5 μm. The mean diameter of the bubbles in the preparation and the bubble concentration remained essentially constant for at least 30 hours. There was no evidence of coalescence, fusion or ripening. The bubble suspension was very stable. Schneider Declaration, ¶ 4.

Echographic examination of the heart of a rabbit followed the injection of 0.1 ml of the '774 patent preparation and showed strong opacification of the right ventricle as well as of the left ventricle. The opacification was very persistent in both ventricles, lasting at least 5 minutes. Schneider Declaration, ¶ 5.

This sample as well as the other stabilized microbubble and microballoon preparations described in the '774 patent are stable for at least weeks or months and they are resistant to fusion, coalescence and ripening, with or without pressure applied. Schneider Declaration, ¶ 6.

A representative sample from the Hilmann patent was prepared by following Example 2 of that patent in all respects. Briefly, 2 ml of an aqueous solution containing 10% by weight Pluronic F-68 was drawn up in a syringe and forcefully injected into 8 ml of an aqueous

solution of glucose (5% by weight) in a 25 ml vial. The gas phase in the vial was air. The mixture was vigorously shaken. Foam was formed during agitation. An aliquot was withdrawn and observed under the light microscope. Schneider Declaration, ¶ 7.

Only a relatively small number of bubbles were detected in the sample and most of them were larger than 10μm. Most of the bubbles burst within seconds. After 1 minute or less almost all of the bubbles had disappeared. After vigorous shaking of the vial, 0.5 ml of this preparation was injected into a rabbit. The heart of the animal was examined by ultrasonography using a 7 MHz probe and an Acuson XP10. Contrast could be detected very transiently (a few seconds) in the right ventricle but no contrast was detectable in the left ventricle. Schneider Declaration, ¶ 8.

Another sample from the Hilmann patent was produced by following Example 2 in all respects except for the use of egg lecithin (final concentration 10 mg/ml) instead of Pluronic F-68. Upon observation under a light microscope, no bubbles were seen. After vigorous shaking of the vial, 0.5 ml of this preparation was injected into a rabbit as previously described. No contrast was detectable in the left ventricle of the rabbit. A few spots of increased contrast could be seen for 1-2 seconds in the right ventricle but there was no complete opacification. Schneider Declaration, ¶ 9. Both bubble suspensions prepared according to Hilmann Example 2 show the typical behavior of free-gas microbubbles, i.e., large size, limited stability. Schneider Declaration, ¶ 10.

The results obtained by Dr. Schneider regarding Hilmann are in fact confirmed by others. In particular, Beller (U.S. Patent No. 5,559,523) showed that preparations prepared according to Hilmann (referred to as EP-B-0 077 752 in Beller) were unable to opacify the left ventricle in the dog. As pointed out by Dr. Schneider, the large size of the bubbles obtained was

most probably the cause since the in vitro experiments showed that the bubbles that were observed were generally above 10 μm in diameter. Bubbles of that size would be trapped in the lungs and would be unable to reach the left ventricle. Schneider Declaration, ¶ 11.

Phospholipid-stabilized bubbles prepared according to U.S. Patent No. 5,413,774 using C_4F_{10} (and even air), show outstanding stability after formation and no significant change in bubble size for periods of at least 44 hours (in the case of air) and 30 hours (for C_4F_{10}). Schneider Declaration, ¶ 12. In contrast, a bubble preparation without the phospholipids or polymers which form the '774 patent's stabilized microbubbles or microballoons, i.e., free-gas microbubbles, are not stable for this length of time and would not be as resistant to fusion, collapse or ripening, whether or not pressure is applied. Schneider Declaration, ¶ 6.

The stability of the stabilized microbubbles disclosed in the '774 patent, both in vitro and in vivo, demonstrates that the stabilized microbubbles of the '774 patent are different from the free gas microbubbles of Hilmann. The ability of the stabilized microbubbles disclosed in the '744 patent to provide substantially greater echogenic contrast also demonstrates the difference between these types of contrast agents. These substantially improved results were unexpected and there is no evidence to suggest that these substantially improved results were expected. Schneider Declaration, ¶¶ 15-17.

As recently held by the Federal Circuit, when an applicant demonstrates substantially improved results, and states that the results are unexpected, this should suffice to establish unexpected results. *In re Soni*, 54 F.3d 746, 751, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995). As Applicants have done this, and there is no evidence to the contrary suggesting that the results would not be unexpected, Applicants' invention as claimed would not have been obvious in view of the references cited by the Examiner.

The '774 reissue application itself also provides definitive evidence of the non-obviousness of the Applicants' claimed invention. *See* Examples 1, 2 and 7 regarding microballoons and Examples 4-6 regarding stabilized microbubbles.

b. Long Felt Need and Failure of Others

In addition to the comparative experiments being submitted, Applicants also submit evidence of long felt need and failure of others in connection with the present patent. The evidence being submitted shows that there was a need for contrast agents for ultrasound imaging procedures, that this need persisted, others failed to satisfy this need, and Applicants were the first to satisfy this need with embodiments of the claims of the subject patent.

It has been well settled by the Court of Appeals for the Federal Circuit that the long felt need for an invention, and the failure of others to satisfy this need, can be strong objective evidence of non-obviousness. *Pro-Mold and Tool Co., Inc. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1572, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). The rationale in recognizing long felt need as an indicator of non-obviousness is that when confronted with a known and substantial need in an industry, the industry would deploy resources to satisfy the need and the need would not persist for a long time if the solution was obvious. *Lyon v. Bausch & Lomb Optical Co.*, 224 F.2d 530, 535, 106 USPQ 1, 5 (2d Cit. 1955), *cert. denied*, 350 U.S. 911 (1955), *reh'g denied,* 350 U.S. 955 (1956); *In re Mahurkar*, 831 F. Supp. 1354, 1377-78, 28 USPQ2d 1801, 1819 (N. D. Ill. 1993). Similarly, evidence of failure of others, either alone or in combination with evidence of long felt need, can be an indicator of non-obviousness in that "[s]uch evidence shows indirectly the presence of a significant defect [in the prior art], while serving as a simulated laboratory test of obviousness of the solution to a skilled artisan." *Symbol Technologies Inc. v. Opticon Inc.*, 935 F.2d 1569, 1578-79, 19 USPQ2d 1241, 1248 (Fed. Cir. 1991).

In establishing a long felt need, courts have considered the following factors as being persuasive: (a) the existence of a persistent and recognized need in the industry as measured from the date of an articulated identified problem, *see Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178, 26 USPQ2d 1018, 1029 (Fed. Cir. 1993); (b) the absence of a key improvement related to the inventor's solution that would have rendered the inventor's solution obvious, *see Newell Co., Inc. v. Kenney Manufacturing Co.*, 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) and (c) the presence of a relationship (*i.e.*, nexus) between the need and claimed invention, *see Sjolund v. Musland,* 847 F. 2d 1573, 1582, 6 USPQ2d 2020, 2028 (Fed. Cir. 1988).[4]

The failure of others, which is most often considered in conjunction with long felt need, can also provide powerful evidence of non-obviousness. In considering evidence of the failure of others, courts weigh heavily the nexus between the failure of others to find a solution to a problem and the problem which the invention purports to solve. *Symbol Technologies Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1248 (Fed. Cir. 1991).

With regard to long felt need and failure of others, Applicants submit herewith the Wheatley Declaration, which substantiates that there has been a long felt need for Applicants'

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[4] A strong nexus exists if the claimed invention satisfies the long felt need. *Id.* at 2028; *In re Cavanagh*, 436 F.2d 491, 496, 168 USPQ 466, 471 (CCPA 1971). However, it is unnecessary for all embodiments encompassed within a claim to satisfy the long felt need. This is because the Federal Circuit has recently held that in connection with a showing of secondary considerations, such as, for example, commercial success, a patentee need not show successful commercialization of all possible embodiments encompassed within a claim in order to rely on the success in the marketplace of an embodiment that was commercialized. *Applied Materials Inc. v. Advanced Semiconductor Materials*, 98 F.3d 1563, 1570, 40 USPQ2d 1481, 1486 (Fed. Cir. 1996). A nexus is also established if the claimed invention is superior to alternative prior solutions in satisfying a need. *Symbol Technologies Inc. v. Opticon, Inc.*, 935 F.2d 1569. 1578, 19 USPQ2d 1241, 1248 (Fed. Cir. 1991).

invention in certain areas of ultrasound imaging, as well as a failure of others in developing solutions to satisfy this need. Wheatley Declaration, ¶¶ 5-12.

Dr. Wheatley states that there was a great need for improved contrast agents for ultrasound imaging of regions of the body, for example, for the detection and diagnosis of diseases and abnormalities. Wheatley Declaration, ¶¶ 5-6. Particularly needed ultrasound contrast agents included those which would be effective in imaging the borders of the right and left chambers of the heart and myocardial perfusion of the heart. Wheatley Declaration, ¶ 5.

As the Wheatley Declaration indicates, others failed to satisfy the need for improved ultrasound contrast agents, particularly in connection with satisfactory imaging of the left ventricle of the heart. Wheatley Declaration, ¶¶ 8-12.

Dr. Wheatley states that certain gas-filled microbubbles and microballoons filled with fluorinated gas such as those of the '774 patent satisfy the aforementioned long felt needs. Wheatley Declaration, ¶ 13.

Applicants were the first to discover '774 patent's claimed stabilized microbubbles and microballoons filled with fluorinated gas that satisfy the forementioned long felt needs. Applicants are not aware of any other party having reduced to practice in the United States or disclosed anywhere the '774 patent's claimed stabilized microbubbles and microballoons which satisfy the aforementioned long-felt needs prior to Applicants' effective filing date.

In conclusion, Applicants respectfully submit that Applicants have presented strong evidence to support that Applicants' claimed invention satisfied certain long felt needs for ultrasound contrast agents. Moreover, Applicants have also presented evidence of failures of others in trying to satisfy these long felt needs. This evidence must be considered by the Patent

Office and is strong indicia that Applicants' claimed invention would not have been obvious to one of ordinary skill of the art at the time Applicants' invention was made.

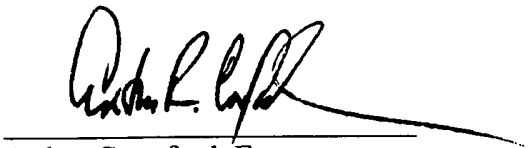
E. CONCLUSION

Applicants respectfully submit that rejected '774 reissue claims 1-7 and 13-48 are directed to subject matter which is novel and non-obvious. As pointed out herein, the cited art neither anticipates nor renders *prima facie* obvious the subject claims. Even assuming a *prima facie* case of obviousness has been established, sufficient rebuttal evidence, including evidence of objective considerations of non-obviousness, has been presented which establishes the patentability of the '774 reissue claims 1-7 and 13-48.

Indeed, prior to anyone else, Applicants disclosed the new methods of making new contrast agents comprising the '774 patent's claimed stabilized microbubbles and microballoons in the context of ultrasound imaging. In so doing, Applicants have achieved an advance in ultrasound imaging which has and will continue to aid in extending the lives of innumerable patients by providing a means for early diagnosis and treatment. It is believed that reissue claims 1-7 and 13-48 are novel and non-obvious and indeed worthy of a patent.

In view of the foregoing, Applicants respectfully request that the rejections of reissue claims 1-7 and 13-48 be withdrawn and all pending claims allowed.

Respectfully submitted,



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